# Viltepso (viltolarsen)

## NOTICE

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## BENEFIT APPLICATION

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This Medical Policy document describes the status of medical technology at the time the document was developed. Since that time, new technology may have emerged or new medical literature may have been published. This Medical Policy will be reviewed regularly and be updated as scientific and medical literature becomes available.

## DESCRIPTION

Viltepso (viltolarsen), an antisense oligonucleotide, is indicated for treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. It is administered once weekly as an intravenous (IV) infusion.

This indication was approved by the Food and Drug Administration (FDA) in August 2020 under accelerated approval based on the surrogate endpoint of an increase in dystrophin in skeletal muscle observed in patients treated with Viltepso (viltolarsen). A clinical benefit of Viltepso (viltolarsen) has not been established.

## POLICY

Viltepso (viltolarsen) is considered **not medically necessary** for all indications, including the treatment for DMD, due to insufficient evidence to demonstrate clinical efficacy.

## CLINICAL RATIONALE

Viltepso (viltolarsen) is an exon-skipping therapy that targets dystrophin pre-messenger ribonucleic acid (mRNA) and induces skipping of mutated exons of the DMD gene that disrupt downstream protein synthesis and lead to nonfunctional or absent dystrophin. Skipping mutated exons results in restoration of small amount of dystrophin. Viltepso (viltolarsen) is indicated for the treatment of DMD in patients with a confirmed mutation amenable to exon 53 skipping which accounts for 8% of DMD population.

**Efficacy**

FDA approval of Viltepso (viltolarsen) was based on a primary endpoint of increased dystrophin production in skeletal muscle during a single phase 2 clinical study in patients who had a confirmed mutation of the DMD gene that was amenable to exon 53 skipping. The trial was not designed to evaluate long-term safety, and no functional outcome, including improved motor function, has been found.

The efficacy of Viltepso (viltolarsen) was evaluated in a phase II, multicenter, two-period, dose-finding trial in male DMD patients with a confirmed diagnosis of DMD amenable to exon 53 skipping (N = 16) (Clemens, 2020). The trial included a 4-week double-blind, randomized, placebo-controlled period followed by a 20-week open-label treatment period. Boys aged 4 years to 9 years from sites in North America were recruited and enrolled in the trial (mean 7 years of age; 15 White patients and 1 Asian patient). Eligible patients were ambulatory with otherwise normal findings on clinical safety laboratory tests. Patients could complete time to stand from supine, time to run or walk 10 m, and time to climb four stairs assessments at screening. Patients were also receiving a stable dose of glucocorticoids for ≥ 3 months prior to enrollment and for the duration of the study. The first study period was a 4-week, double-blinded, randomized, placebo-controlled period in which patients were randomized 3:1 to receive Viltepso (viltolarsen) or placebo. Patients assigned to Viltepso (viltolarsen) received 40 mg/kg weekly (low-dose cohort; n = 6) or the FDA-approved dose of 80 mg/kg weekly (high-dose cohort; n = 5). Patients and study teams were informed regarding the dose cohort. After completion of the first 4 weeks, all patients received Viltepso (viltolarsen) according to the assigned cohort dose for a 20-week open-label treatment period.

The primary study outcomes were safety, tolerability, and pharmacokinetics (Clemens, 2020). Muscle dystrophin production was also assessed by Western blot for the primary study efficacy outcome. Additional secondary efficacy outcomes were gross motor skill assessments of timed function tests, including time to stand from supine, time to run/walk 10 m, time to climb four stairs, and 6-minute walk test as well as muscle testing. An external matched natural history control group provided by the Cooperative International Neuromuscular Research Group Duchenne Natural History Study was used to compare timed function and strength evaluations. At the week 25 posttreatment muscle biopsy following 4 weeks of Viltepso (viltolarsen) or placebo and 20 weeks of open-label Viltepso (viltolarsen), all patients showed significant increases in dystrophin content, with a significant difference between baseline and posttreatment biopsies observed in both treatment groups (Clemens, 2020). Baseline mean dystrophin levels normalized to myosin heavy chain and expressed as a percentage of normal dystrophin levels for both the low-dose group and high-dose group were 0.3% and 0.6%. At week 25, mean percentage of normal dystrophin level for the low-dose group was 5.7% and 5.9% for the high-dose group. For the low-dose cohort, there was a change from baseline in dystrophin normalized to myosin heavy chain of 5.4% ($p < 0.001$). For the high-dose cohort, the change from baseline in dystrophin normalized to myosin heavy chain was 5.3% ($p = 0.01$).

In an evaluation of disease progression using timed function tests and muscle strength assessments, comparison of Viltepso (viltolarsen)-treated patients with the external comparator group demonstrated an

improvement or stabilization of function over the 25-week period for the Viltepso (viltolarsen) group compared with a decline for the external comparator group for all timed function tests except for the time to climb four stairs. Mean velocity in the time to run/walk 10 m test significantly improved at week 25 in the Viltepso (viltolarsen) group compared with a decline in the external comparator group (change from baseline of 0.23 m/s vs. -0.04 m/s, respectively; p = 0.003). The 6-minute walk test showed significant improvement at week 25 for the Viltepso (viltolarsen) group compared with a decline in the external comparator group (change from baseline of 28.9 m vs. −65.3 m; p = 0.047). Significant improvements in time to stand from supine were also observed for the Viltepso (viltolarsen) group compared with the external comparator group (change from baseline at 25 weeks of −0.19 s vs. 0.66 s; p = 0.046). However, there was no significant difference between the Viltepso (viltolarsen) group and the external control group for change in velocity in the time to stand from supine test or change in time to climb four stairs test. There were also no differences between the Viltepso (viltolarsen) group and the external comparator group in measures of muscle strength by isometric testing.

**Safety**

The majority of patients experienced treatment-emergent adverse events during the single phase 2 clinical trial, though no treatment-emergent serious adverse events were reported (Clemens, 2020). In the double-blind period, no single treatment-emergent adverse event was reported in more than one patient. The most common treatment-emergent adverse events in the open-label study period were cough and nasopharyngitis (25% each). Most patients with treatment-emergent adverse events recovered by the end of the study, and the unresolved adverse events in two remaining patients were deemed to be mild in severity. Viltepso (viltolarsen) contains a warning for kidney toxicity, although this has not been observed in previous clinical studies.

Anti-dystrophin antibodies were detected in 1 out of 16 patients (6.25%) at weeks 13 and 24; however, at week 37, week 49, week 73, and week 97, no anti-dystrophin antibodies were detected in the same patient. This patient also achieved a change from baseline in dystrophin levels that was comparable to the mean change in the patient's dosage group (80 mg/kg/week), and there were no adverse events reported with this antibody production. In another trial, all samples collected from the 16 patients were determined to be both anti-viltolarsen antibody and anti-dystrophin antibody negative. Overall, there was a lack of observed immunogenicity.

**Other**

In a single open-label, multicenter, parallel-group, phase 1/2 exploratory study conducted in Japan, Viltepso (viltolarsen) was investigated for its ability to induce dystrophin expression and its safety was monitored during treatment in patients with a DMD gene mutation amenable to exon 53 skipping. 16 ambulant and nonambulant males aged 5-12 years with DMD received viltolarsen 40 or 80 mg/kg/week via intravenous infusion for 24 weeks. Primary endpoints were dystrophin expression and exon 53 skipping levels. In western blot analysis, mean changes in dystrophin expression (% normal) from baseline to Weeks 12 and 24 were - 1.21 (P = 0.5136) and 1.46 (P = 0.1636), respectively, in the 40 mg/kg group, and 0.76 (P = 0.2367) and 4.81 (P = 0.0536), respectively, in the 80 mg/kg group. The increase in mean dystrophin level at Weeks 12 and 24 was significant in the 80 mg/kg group (2.78%; P = 0.0364). Patients receiving 80 mg/kg showed a higher mean exon 53 skipping level (42.4%) than those receiving 40 mg/kg (21.8%). All adverse events were judged to be mild or moderate in intensity and none led to study discontinuation.

As part of the FDA's accelerated approval of Viltepso (viltolarsen), a post-marketing confirmatory study titled RACER53 is currently enrolling patients. It is a placebo-controlled study that must assess whether

Viltepso (viltolarsen) improves motor function of DMD patients with a confirmed mutation of the dystrophin gene amenable to exon 53 skipping. It is expected to conclude by 2024. If a clinical benefit is not found, the FDA may withdraw approval.

In summary, the clinical benefit of treatment for DMD with Viltepso (viltolarsen) has not been demonstrated. The establishment of a clinical benefit, including improved motor function and pulmonary function, is warranted in on-going clinical trials. The following conclusion is also stated in the FDA prescribing information, "Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials."

## PROCEDURES AND BILLING CODES

***To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.***

- C9071 – Injection, viltolarsen, 10 mg (cancelled 04/01/2021)
- J1427 – Injection, viltolarsen, 10 mg (effective 04/01/2021)

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## POLICY HISTORY

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